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## Complement activation in chronic kidney disease and dialysis

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*Document Version*

Publisher's PDF, also known as Version of record

*Publication date:*

2019

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Gaya da Costa, M. (2019). *Complement activation in chronic kidney disease and dialysis*. [Thesis fully internal (DIV), University of Groningen]. Rijksuniversiteit Groningen.

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# CHAPTER

# 1

## General Introduction

## Introduction

Chronic kidney disease (CKD) is a growing global health problem with a prevalence of approximately 10–15% worldwide.<sup>1</sup> Diabetes and high blood pressure are the main causes of CKD.<sup>2</sup> In the Netherlands, 2000 new patients are diagnosed with CKD each year. Progression of the disease leads to end-stage renal disease (ESRD), which then requires renal replacement therapy as a treatment. Renal transplantation is the preferred treatment for ESRD, however not all patients are considered suitable for transplantation and not all the suitable patients can immediately be transplanted due to an organ shortage. Therefore, most of the ESRD patients remain in dialysis for life-long treatment or until an appropriate organ for renal transplantation is found. In the Netherlands, 6.500 patients are dependent on dialysis of which the majority receives hemodialysis (HD). Although dialysis is a life-saving treatment, the life expectancy and the quality of life of these patients is inferior when compared to the general population. Every year, 1 out of 6 dialysis patients die. Moreover, from the patients that start dialysis at the age of 45 to 65 years old, 50% will die within 5 years.<sup>3</sup> Compared to the general population, HD patients have a 10–20 fold increased risk of cardiovascular morbidity and mortality.<sup>4,5</sup> The traditional risk factors of cardiovascular (CV) disease such as hypertension, diabetes and dyslipidemia do not seem to be the responsible for the increased CV- risk since studies targeting modifications in these risk factors were unsuccessful.<sup>6</sup> However, the non-traditional risk factors for CV disease include inflammation, oxidative stress and vascular calcification and are associated with poorer prognosis.<sup>6</sup> The complement system has been proposed to play a vital role in the inflammatory response induced by dialysis and could be the missing link between high morbidity and mortality and dialysis therapies.<sup>6,7</sup> As a major part of the innate immune system, the complement system consists of a network of more than forty proteins. Initially, the complement system was perceived as a system to fight against pathogens. However, this traditional view of the complement system has evolved over the past years. Besides fighting against pathogens, the complement system has been linked to different disease processes and was shown to be crucial for homeostasis.<sup>8,9</sup> In this thesis, we further investigate the role of the complement system in different contexts, from health to disease and treatment.

## Scope of the thesis

The aim of this thesis is to investigate the pathophysiology and clinical consequences of complement activation in CKD and dialysis. Furthermore, this thesis aims to unravel the mechanisms and pathways involved in complement activation in CKD and dialysis. **Chapter 2** offers an overview of the role of the complement system in renal disease with a special focus on the lectin pathway. A new concept of lectin pathway activation was discussed and a fresh look into complement related renal diseases was given. In **Chapter 3**, the current knowledge about the role of the complement system in dialysis was summarized. Based on previous literature, a model for complement activation in hemodialysis and peritoneal dialysis was proposed. In addition, the clinical consequences of complement activation were discussed and potential therapeutic options were explored. In **Chapter 4**, we investigated if complement activation still occurs in hemodialysis with modern membranes. In addition, we explored the effect of hemodialysis on complement components of the different



pathways. Lastly, we assessed whether these changes were associated with morbidity and mortality in HD patients. Next, in **Chapter 5** we hypothesized that HD-induced complement activation initiates a pro-inflammatory and pro-thrombotic response. A case-control study was performed to investigate intradialytic complement activation in patients that developed cardiovascular disease during follow-up and compared this to patients who remained disease free. Furthermore, inflammation and pro-thrombotic factors were also assessed. To explore the causal relation between complement activation and subsequent inflammation and coagulation, we developed an *ex-vivo* model of HD and tested the effect of complement inhibition on inflammation and coagulation. In **Chapter 6**, we investigated whether systemic and local complement activation occurred in peritoneal dialysis (PD) and dissected the pathways responsible for it. We hypothesized that while HD would be associated with systemic complement activation, PD would only activate the complement system locally. Moreover, we compared complement activation in PD with complement activation in HD and with CKD patients to exclude the possibility of complement activation due to the disease itself. Lastly, we investigated the role of soluble CD59 in local complement activation by PD. In **Chapter 7** we explored the *in-vitro* capacity of different iron preparations to activate the complement system. Iron preparations are commonly used in CKD and are known for their risk of hypersensitivity reactions. Previously, the complement system has been proposed to be the key element in the development of the hypersensitivity reactions through complement activation-related pseudo-allergy (CARPA). Therefore, to test the concept of CARPA, in **Chapter 7** different iron preparations were tested in multiple complement assays. Subsequently, in **Chapter 8** two of the most commonly clinically used iron preparations were tested *in-vivo*.

Currently, complement inhibitors are being used in the clinics and more are expected to follow since several clinical trials are ongoing. Nevertheless, patient selection remains crucial for the clinical success of these treatments, considering the heterogeneity of complement mediated-diseases together with the high costs of complement therapeutics. Besides genetics, patient characteristics such as age and sex could be valuable to select patients that would benefit from complement-targeted therapies. Therefore, **Chapter 9** explores age and sex-associated changes in the complement system in a healthy Caucasian population.

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